EXHIBIT 3

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KAI-UWE BALDENIUS, CHRISTINE BECK, HANS-PETER HARZ, MARKUS LOHSCHEIDT, and DANIELA KLEIN

Appeal 2007-2604
Application 10/468,609
Technology Center 1600

Decided: January 15, 2008

Before DONALD E. ADAMS, DEMETRA J. MILLS, and NANCY J. LINCK, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge.*

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1 and 5-19, which are all the claims pending in the application.

The Examiner recognizes that this Appeal is related to Application 10/468,562, Appeal 2006-3250. According to the Examiner, the subject matter of Appeal 2006-3250 "is very similar to the instant claimed

invention, as each application claims a method of producing D-pantothenate salts by fermenting a bacterium of the family Bacillaceae. The difference is the purification method in each application - cation exchange in the instant application vs. anion exchange in the copending application" (Answer 2). On January 26, 2007, a Decision on Appeal 2006-3250 was entered into the record of Application 10/468,562 reversing the rejection of record.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

1. A process for preparing D-pantothenic- acid and/or salts thereof which comprises

   a) fermenting at least one bacterium from the Bacillaceae family which produces D-pantothenic acid and in which the biosynthesis of pantothenic acid (pan) and/or isoleucine/valine (ilv) is deregulated and which forms at least 2 g/l of salts of D-pantothenic acid by fermentation in a culture medium, wherein no free β-alanine and/or β-alanine salt is fed to the culture medium,

   b) passing the D-pantothenate-containing fermentation solution through a cation exchanger, free D-pantothenic acid being formed from the salts of D-pantothenic acid,

   c) adding a calcium base and/or magnesium base to set the free D-pantothenic acid-containing solution to a pH of 3-10, a solution or suspension being obtained which contains calcium and/or magnesium pantothenate and

   d) subjecting the calcium pantothenate- and/or magnesium pantothenate-containing solution to drying and/or formulation.

The references relied upon by the Examiner are:

Hikichi	US 5,518,906	May 21, 1996
Binder	US 6,582,939 B1	Jun. 24, 2003

Baigori et al. (Baigori), "Isolation and Characterization of *Bacillus subtilis* Mutants Blocked in the Synthesis of Pantothenic Acid," *J Bacteriology*, 173(13): 4240-4242 (1991)

Sorokin et al. (Sorokin), "Sequence analysis of the *Bacillus subtilis* chromosome region between the *serA* and *kdg* loci cloned in a yeast artificial chromosome," *Microbiol.*, 142: 2005-2016 (1996)

GROUND OF REJECTION

Claims 1 and 5-19 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Hikichi, Baigori, and Binder.

We reverse.

DISCUSSION

"Pantothenic acid is a commercially important vitamin that is used in cosmetics, medicine, human nutrition and in animal nutrition" (Binder, col. 1, ll. 19-21). D-pantothenate can be prepared chemically or biologically (Binder, col. 1, ll. 22-24). Binder teaches that DL-pantolactone is an important compound in the chemical synthesis of D-pantothenate (Binder, col. 1, ll. 24-29). DL-pantolactone is prepared in a multi-step process that includes separating D-pantolactone from the racemic mixture before it is condensed with β-alanine to yield D-pantothenic acid (*id.*; *see also* Hikichi, column 1, line 14 - column 2, line 19). As Hikichi points out, the difficulties in resolving the racemic pantolactone mixture is one of a number of

drawbacks associated with the art recognized methods for chemically synthesizing D-pantothenic acid (Hikichi, col. 1, l. 62 - col. 2, l. 19).

In contrast to the chemical synthesis methods, the production of D-pantothenic acid biologically, through the fermentation of microorganisms, provides for the direct production of the D-pantothenic acid thereby avoiding the additional resolution steps required by chemical synthesis methods (*see e.g.*, Binder, col. 1, ll. 30-33; *see also* Hikichi, col. 3, ll. 8-14). Nevertheless, while Appellants recognize that a number of fermentation processes are known in the art for preparing D-pantothenic acid, Appellants point out that these processes suffer from a number of disadvantages, such as low D-pantothenate yield or the requirement for the addition of β-alanine (Specification 1-3)[1]. Therefore, Appellants disclose that "[i]t is an object of the present invention to provide an . . . improved process for preparing D-pantothenic acid and/or salts thereof which does not have the abovementioned disadvantages. For economical reasons, a process is desirable here in which supplying β-alanine is greatly decreased or is not required at all" (Specification 3).

Accordingly, Appellants' claimed invention is directed to a process for preparing D-pantothenic acid and/or salts thereof. The process set forth in claim 1 comprises four required steps.[2] The first step requires that at least

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[1] While Appellants' Specification does not discuss Hikichi or Binder, both of these patents disclose the fermentation of a microorganism to produce D-pantothenate. We note, however, that both of these patents require the addition of β–alanine (*see* Hikichi, col. 2, ll. 20-24; Binder, col. 8, ll. 32-34).

[2] All of the remaining claims before us on appeal ultimately depend from claim 1.

one bacterium is fermented to form at least 2 g/l of salts of D-pantothenic acid in a culture medium to which no free β-alanine and/or β-alanine salt is added. This step places three requirements on the bacterium: (1) the bacterium must be from the Bacillaceae family; (2) the bacterium must produce D-pantothenic acid; and (3) the bacterium is modified so that the biosynthesis of pantothenic acid (pan) and/or isoleucine/valine (ilv) is deregulated. According to Appellants' Specification, "[t]he word 'deregulation', for the purposes of the present invention, means changing or modifying at least one gene which codes for one enzyme in a biosynthetic metabolic pathway, so that the activity of the enzyme is changed or modified in the microorganism" (Specification 7). Included among the various modifications contemplated by Appellants' disclosure is deregulating the biosynthesis of pantothenic acid (pan) and/or isoleucine/valine (ilv) by "increasing the number of copies of the gene in the genome or by introducing a varying number of copies of plasmids" (Specification, page 8).

The second step of Appellants' process requires that the D-pantothenate-containing fermentation solution be passed through a cation exchanger, whereby free D-pantothenic acid is formed from the salts of D-pantothenic acid.

The third step of Appellants' process requires that a calcium and/or magnesium base be added to the D-pantothenic acid-containing solution to set the solution to a pH of 3-10, thereby obtaining a solution or suspension which contains calcium and/or magnesium pantothenate.

The final step in Appellants' process requires that the calcium and/or magnesium pantothenate-containing solutions is dried and/or formulated.

According to the Examiner, the process outlined above, would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made in view of the combination of Hikichi, Baigori, and Binder (Answer 3-7).

It is clear from Appellants' Specification that a number of microorganisms are capable of producing D-pantothenic acid (Specification 5-6; *see also* Hikichi col. 3, ll. 39-50; Baigori 4240; and Binder, col. 1, ll. 34-43). Figure 1 of Baigori outlines the metabolic pathway for the production of D-pantothenate in *E. coli* and *S. typhimurium* (Baigori 4241: FIG. 1)[3]. In addition, Baigori teach a number of genes involved in the synthesis of D-pantothenate, which include *pan* B, *pan* C, *pan* D, and *pan* E (*id.*; *see also* Hikichi, col. 7, ll. 27-31).

According to the Examiner, Hikichi discloses a fermentation method for producing D-pantothenic acid or calcium D-pantothenate (Answer 3). In this regard, the Examiner finds that Hikichi discloses a method wherein E. coli are cultured in the presence of β-alanine, then passing the culture medium over a cation exchange column and neutralizing the resulting solution with $Ca(OH)_2$ (Answer 3-4). The Examiner finds that Hikichi teaches that "[t]o improve purity and yield, calcium chloride may [be] added to this solution to produce high purity calcium D-pantothenate . . . which may be dried" (Answer 4).

The Examiner recognizes, however, that Hikichi differs from Appellants' claimed invention by not disclosing, *inter alia,*

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[3] Baigori also teaches that *S. typhimurium* is capable of reducing ketopantoate to pantoate by both ketopantoate reductase (the product of the *pan* E gene) and acetohydroxy acid isomerase (the product of the *ilv*C gene) (Baigori 4241: col. 1 - col. 2, bridging paragraph).

1. the use of an organism of the Bacillaceae family (e.g., *Bacillus subtilis*); or
2. the use of a culture medium that does not contain β-alanine (*id.*).

To make up for these deficiencies in Hikichi, the Examiner relies on Baigori to teach that *Bacillus subtilis* "produces its own β-alanine from aspartic acid" and that D-pantothenic acid can be produced by culturing *Bacillus subtilis* in the absence of β-alanine (*id.*). The Examiner, however, fails to appreciate that Baigori also teaches that *E. coli*, the bacteria used by Hikichi, also produces its own β-alanine from aspartic acid (Baigori 4241: FIG. 1). Further, while *E. coli* produces its own β-alanine, Hikichi requires that the culture medium be supplemented with β-alanine in order to produce large quantities of D-pantothenic acid (Hikichi, col. 2, ll. 20-24 and col. 3, ll. 58-61).

Nevertheless, the Examiner reasons that since both *E. coli* and *Bacillus subtilis* produce D-pantothenic acid, a person of ordinary skill in the art at the time the invention was made would have found it prima facie obvious to substitute *Bacillus subtilis*, for *E. coli* in the method taught by Hikichi (Answer, page 4). According to the Examiner a person of ordinary skill in the art would have been motivated to make this substitution to avoid adding β-alanine to the culture medium (Answer 5). We disagree.

Even if a person of ordinary skill in the art would have been modified Hikichi's method by substituting *Bacillus subtilis* for *E. coli*, there is no suggestion in either reference that one would obtain at least 2 g/l of salts of D-pantothenic acid without supplementing the fermentation media with additional β-alanine. The Examiner admits as much by recognizing that "one of ordinary skill in the art would not have known in advance exactly

how much pantothenic acid would have been produced in a recombinant fermentation with *B. subtilis* as a host cell in which no β-alanine is added" (Answer 5-6). While it is true that both organisms produce their own β-alanine, as discussed above, Hikichi requires that the culture medium be supplemented with β-alanine in order to produce large quantities of D-pantothenic acid. Accordingly, we disagree with the Examiner's assertion that due to the similarities between *E. coli* and *B. subtilis* with respect to D-pantothenic acid synthesis, the skilled artisan would have expected to have produced at least 2 g/L (Answer 6). The Examiner provides no evidentiary basis to support this assertion. [4]

[4] As the Examiner recognizes Hikichi "did not measure the amount of pantothenic acid produced by their bacteria in a medium containing no β-alanine" (Answer 12). Therefore it is unclear from this record why a person of ordinary skill in the art would have expected to produce at least 2 g/l of D-pantothenic acid by culturing *B. subtilis* in a medium lacking β-alanine as the Examiner suggests. While the Examiner's asserts that Hikichi did measure the amount of pantoic acid produced by bacteria in a medium containing no β-alanine (*id.*), the Examiner provides no evidence to suggest that there is a relevant (e.g., 1:1) relationship between the amount of pantoic acid and the amount of D-pantothenic acid produced by the bacteria in the absence of a culture medium supplemented with β-alanine. Contrary to the Examiner's intimation, the evidence on this record teaches that in order to produce D-pantothenic acid the bacteria must be fermented in a culture medium containing β-alanine (*see* Hikichi, col. 3, ll. 58-61 and col. 13-14, examples 3 and 4; and Binder, col. 8, ll. 32-34).

We recognize the Examiner's assertion that since Baigori teaches the genes involved in the biosynthetic pathway of D-pantothenic acid[5], "one of ordinary skill in the art would have known how to manipulate the expression of these genes to substantially increase the production of pantothenic acid, because such genetic manipulation was used in may other cases to increase the expression of genes" (Answer, page 5). We agree that a person of ordinary skill in the art would have appreciated that the genes involved in biosynthesis of D-pantothenic acid could have been manipulated.

In this regard, we recognize that Hikichi discloses a method for the production of D-pantothenic acid "wherein said microbe is a microbe transformed with a plasmid DNA carrying the region of a gene involved in biosynthesis of pantothenic acid . . . or a part of the region" (Hikichi, col. 2, l. 66 - col. 3, l. 3). Stated differently, Hikichi teaches the use of a bacteria wherein the biosynthetic pathway of pantothenic acid is deregulated by introducing a varying number of copies of plasmids (*Cf.* Specification 7-8: bridging paragraph).

In particular Hikichi discloses that "[t]he gene involved in the pantothenic acid biosynthesis mentioned herein is the panB, panC or panD gene, corresponding to the enzymes ketopantoate hydroxymethyltransferase, pantothenate synthetase and aspartate-α-decarboxylase, respectively" (Hikichi, col. 7, ll. 27-31). We note, however, that while Hikichi discloses the "deregulation" of one or more of the genes involved in the biosynthetic

[5] We recognize the Examiner's reliance on Sorokin to teach the sequences of the *B. subtilis* genes involved in the synthesis of pantothenic acid (Answer 10-11). According to the Examiner, Sorokin confirms "the teaching of Baigori et al. that *B. subtilis* and *E. coli* share a common pantothenic acid synthesis pathway" (Answer 11).

pathway of D-pantothenic acid, Hikichi still requires that the organism be grown in a medium that contains β-alanine in order to obtain large amounts of D-pantothenic acid (*see e.g.*, Hikichi, col. 3, ll. 58-61 and col. 13-14, examples 3 and 4).

Therefore, we agree with the Examiner that a person of ordinary skill in the art could not have predicted, from the combination of Hikichi and Baigori, "exactly how much pantothenic acid would have been produced" by culturing a microorganism modified to contain a gene or genes involved in the involved in the biosynthesis of pantothenic acid in the absence of β-alanine (Answer 5-6). Accordingly, we disagree with the Examiner that due to the similarities between *E. coli* and *B. subtilis* with respect to D-pantothenic acid synthesis, the skilled artisan would have expected to have produced at least 2 g/L by fermenting *B. subtilis* in the absence of β-alanine (Answer 6). We find no evidence on this record to support this assertion. To the contrary, the evidence on this record teaches the addition of β-alanine to the culture medium is required. In this regard, we note that the United States Supreme Court recently stated that the analysis under 35 U.S.C. § 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). However, in emphasizing this flexible approach to the obviousness analysis, the Court also reaffirmed the principle that claims would likely be unobvious when "when the prior art teaches away" from their practice. *Id.* at 1740.

As for Binder, the Examiner finds that Binder discloses that in a method of producing D-pantothenic acid from bacteria or yeast, the calcium

or magnesium salts of D-pantothenate are produced at the end of the culture phase by adjusting the pH "by adding a solution or suspension of an alkaline earth-containing compound, such as $Ca(OH)_2$ or $Mg(OH)_2$, . . . at a concentration of 5-50 wt. %" (Answer 6). Binder, however, fails to make up for the deficiencies in the combination of Hikichi and Baigori. On the contrary, Binder complements Hikichi by disclosing a method of producing D-pantothenic acid by fermenting the bacteria in the presence of β-alanine (Binder, col. 8, ll. 32-34).

For the foregoing reasons we reverse the rejection of claims 1 and 5-19 under 35 U.S.C. § 103 as being unpatentable over the combination of Hikichi, Baigori, and Binder.

CONCLUSION

In summary, we reverse the rejection of record.

REVERSED

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte H. GARRETT WADA, and MATTHEW B. MURPHY

Appeal 2007-3733
Application 10/613,220
Technology Center 1600

Decided: January 14, 2008

Before DEMETRA J. MILLS, ERIC GRIMES, and FRANCISCO PRATS, *Administrative Patent Judges.*

PRATS, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a system for detecting a component of interest in a biological sample. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

THE INVENTION

Detecting a DNA molecule or protein of interest in a biological sample is "of fundamental value in, e.g., diagnostic medicine, archaeology,

anthropology and modern criminal investigation" (Spec. 1). Thus, the Specification discloses "devices, systems, and kits for detecting a component of interest in a complex mixture" (*id.* at 2).

Claims 1-23 are pending and on appeal (App. Br. 2).[1] Claim 1 is representative and reads as follows:

> 1. A system for detecting a component of interest in a sample, the system comprising:
>
> (i) a microfluidic device comprising:
>
> (a) a first microscale channel comprising a gel filled component separation region;
>
> (b) a second microscale channel downstream from the first channel that is fluidly coupled to the first channel, the second channel configured to contain a particle set therein;
>
> (c) a binding region fluidly coupled to or within the first channel;
>
> (d) a source of a component-binding moiety fluidly coupled to the binding region which is capable of binding to the component of interest;
>
> (e) a first detection region within the first channel; and
>
> (f) a second detection region within the second channel which includes a particle stacking region within the second detection region;
>
> (ii) a fluid direction system fluidly coupled to the microfluidic device, which fluid direction system is configured to transport the sample through at least the first and second microscale channels;
>
> (iii) a control system operably linked to the fluid direction system, which control system is configured to instruct the fluid direction system to deliver or transport the sample through at least the first and second microscale channels; and

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[1] Appeal Brief filed February 8, 2007.

(iv) a detection system which is configured to be positioned proximal to the first and second detection regions.

THE REJECTION

The Examiner applies the following documents in rejecting the claims:

Nelson	US 6,007,690	Dec. 28, 1999
Spence	US 6,540,895 B1	Apr. 1, 2003

The following rejection is before us for review:

Claims 1-23 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Nelson and Spence. (Ans. 3-5).

ISSUE

The Examiner cites Nelson as disclosing "microfluidic devices comprising several alternative embodiments" (Ans. 3). The Examiner contends that several of Nelson's embodiments meet most of the limitations recited in claim 1 for the microfluidic device (*see id.* at 3-4).

The Examiner concedes that Nelson "does not particularly point out a control system linked to the fluid direction system" (*id.* at 4). Pointing out that Spence "teaches cell sorting utilizing microfluidic systems controlled by a computer or microprocessor that control fluid flow," the Examiner contends that one of ordinary skill would have considered it obvious "to modify the teachings of Nelson et al to include a control system to instruct fluid direction as taught by Spence et al because procedures can be programmed using any suitable software that can perform a variety of functions" (*id.* at 5 (citing Spence, col. 15, ll. 5-27)).

Appellants contend that neither of the cited references discloses or suggests all of the limitations in claim 1 (App. Br. 5). Specifically,

Appellants argue that they "are unable to identify any structure taught by Nelson that corresponds to Applicants' claimed 'source of a component-binding moiety fluidly coupled to the binding region'" (Reply Br. 5). Appellants further contend that "Spence is silent with regard to a channel comprising a gel filled component separation region and so cannot teach a source of a component-binding moiety fluidly coupled to a binding region that is fluidly coupled to or within such a channel" (*id.* at 5-6).

The issue with respect to this rejection, therefore, is whether the Examiner has shown that a device having the configuration of features recited in claim 1, including the "source of a component-binding moiety fluidly coupled to the binding region," would have been obvious to one of ordinary skill in the art.

FINDINGS OF FACT

1. Claim 1 recites a system having the following components:

(i) a microfluidic device having a specified arrangement of two channels and several regions;

(ii) a fluid direction system fluidly coupled to the microfluidic device, the fluid direction system being configured to transport a fluid sample through the two channels;

(iii) a control system operably linked to the fluid direction system, the control system being configured to instruct the fluid direction system to transport the sample through the two channels; and

(iv) a detection system configured to be positioned proximal to first and second detection regions in the microfluidic device.

2. Claim 1 requires the microfluidic device component to have:

(a) a first microscale channel having a gel-filled region for separating components within a sample;

(b) a second microscale channel downstream from the first channel, the second channel being fluidly coupled to the first channel and also configured to contain a particle set;

(c) a binding region which is fluidly coupled to the first channel, or which is within the first channel;

(d) a source of a component-binding moiety fluidly coupled to the binding region, the component-binding moiety being capable of binding to a component of interest;

(e) a first detection region within the first channel; and

(f) a second detection region within the second channel, the second detection region including a particle stacking region.

3. Because the "source of a component-binding moiety . . . capable of binding to the component of interest" must be "fluidly coupled to the binding region," we interpret claim 1 as requiring the "source" to be a separate structure from the binding region. This interpretation is consistent with the Specification, which discloses a particle well 112, fluidly coupled to binding channel 110 (Spec. 12; *see also* Figure 1). The Specification discloses that the "particle set is released from particle well 112 into binding channel 110. The particle set with the components [of interest] attached or adsorbed onto the particle member types is then directed to detection region 114, where the particle member types of the particle set are optionally stacked" (Spec. 12; *see also* Figure 1).

4. Nelson describes microfluidic devices useful in separating and detecting compounds of interest in a number of applications, including "high throughput screening, for genomics and pharmaceutical applications such as gene discovery, drug discovery and development, and clinical development; for point-of-care in vitro diagnostics; for molecular genetic analysis and nucleic acid diagnostics; for cell separations including cell isolation and capture; and for bioresearch generally" (Nelson, col. 2, ll. 61-67). Nelson's devices comprise "at least an enrichment channel and a main electrophoretic flowpath . . . . The enrichment channel serves to enrich a particular fraction of a liquid sample for subsequent movement through the main electrophoretic flowpath" (Nelson, col. 2, ll. 48-53).

5. Nelson discloses a number of elements that correspond to claim 1's "component-binding moiety." Specifically, Nelson discloses that the enrichment channel can contain component-binding materials such as affinity adsorbents, metal chelating agents, Protein G, or antibodies, which can be bound to matrices of insoluble particles, or be membrane-bound (*see* Nelson, col. 5, l. 12, through col. 6, l. 53). Nelson discloses an example in which antibody-coated magnetic beads are used to bind to desired targets in the enrichment zone (*id.* at col. 21, l. 13, through col. 22, l. 13 (Example 2)). Nelson also exemplifies using magnetic beads to bind DNA in the enrichment zone (*id.* at col. 22, l. 15, through col. 23, l. 54 (Example 3)).

6. Nelson also discloses that, in certain embodiments, "affinity zones" can be placed in the main electrophoretic path to capture components of interest (Nelson, col. 17, ll. 9-33; col. 18, ll. 28-32; *see also* Figures 16 and 18). The affinity zones may contain the DNA-specific or protein-specific binding moieties similar to those used in the enrichment channel (*id.* at col.

17, ll. 33-47). Nelson does not disclose a separate reservoir or "source" for the component-binding moieties in either the enrichment channel or the main electrophoretic flowpath.

PRINCIPLES OF LAW

> As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):
>
> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . . After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

When determining whether a claim is obvious, an examiner must make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). Moreover, as the Supreme Court recently stated, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added)).

ANALYSIS

We agree with Appellants that the Examiner has not explained where or why the cited references disclose or suggest a microfluidic device having a "source" for the component-binding moieties, wherein the source is separate from a binding region fluidly coupled to or within the first channel.

We note, as pointed out by the Examiner, that Nelson discloses the use of particle-borne component-binding moieties in different parts of its various microfluidic devices (*see* Findings of Fact 6 and 7, above).

However, Nelson's component-binding moieties are intended to remain in either the enrichment zone or affinity zones, with the component of interest being eluted therefrom (*see, e.g.,* Nelson at col. 21, l. 13, through col. 22, l. 13 (Example 2); col. 22, l. 15, through col. 23, l. 54 (Example 3)). Thus, since Nelson's component-binding moieties do not appear to move from their designated zones within the device, we see no apparent specific reason why a person of ordinary skill would have given Nelson's device a separate source of material to replenish the component-binding moieties. Moreover, we do not see any clearly articulated reasoning from the Examiner explaining why one of ordinary skill viewing the cited references would have considered it obvious for Nelson's device to contain a separate source, or reservoir, for the component-binding moieties.

It is well settled that the "Patent and Trademark Office (PTO) must consider all claim limitations when determining patentability of an invention over the prior art." *In re Lowry*, 32 F.3d 1579, 1582 (Fed. Cir. 1994). Because the Examiner has not explained why every limitation in claim 1 would have been obvious to a person of ordinary skill in the art, we agree with Appellants that the Examiner has not made out a case of prima facie obviousness. We therefore reverse the Examiner's obviousness rejection of claims 1-23.

REVERSED

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